REMARKS

Allowed Claims

Applicants appreciate the Examiner's Allowance of Claims 1-54, 75-77 and 97-107.

Claim Amendments – Reference to Disclosure

As explained in depth below, while Applicants respectfully traverse the rejections in the January 11, 2005 Office Action, in order to advance the prosecution of this application, independent Claim 55 has been amended so as to be directed to one embodiment of the present invention.[1]

In particular, this claim is now more explicitly directed to one embodiment of the method of the present application, i.e. a method of treating tissue using a single light source having a pulse duration of greater than 10 microseconds. In addition, Claim 57 has been amended, and Claims 62-63 and 66-67 canceled, in order to bring the set of claims dependent on Claim 55 into conformity with independent Claim 55. As explained below, the features of Claim 55 are clearly supported by the application as filed.

Examples in support of the embodiment of this claim, i.e. a method of treatment using a single light source yielding a duration light application of at least 10 microseconds, are found in the specification and drawings of the present application as follows. For instance, the present application describes treatment to promote thermal overload of pigmented tissue in the following terms:

> "The inventors of the present application have discovered a process to kill pigmented tumor cells by thermally overloading them whereas the relatively unpigmented cells in healthy tissues surrounding the tumor are spared. Figs. 9 and

[1] The allowed claims are not limited to this embodiment.

10 illustrate such an alternate embodiment for the present invention wherein a focused light beam 86 (Fig. 9) and a non-focused light beam 96 (Fig. 10), respectively, are used to kill pigmented tumor cells 98. Such pigmented tumor cells 98 may be located at the surface of tissue 92 to be treated, or may be located significantly below the surface. Illumination of pigmented tumor cells 98 may be effected using a *continuous wave or pulsed laser source* operating in either of two wavelength bands between approximately 450 and 800 nm and between approximately 800 and 1400 nm." (p. 24, lines 13-22, emphasis added)

Reference to Figures 9 and 10 shows that a single source (80) is used to produce the therapeutic light beam (86 or 96) that is directed onto tissue to be treated. As noted in this passage, applicable light sources include continuous wave or pulsed laser sources. A listing of applicable light sources is provided elsewhere in the specification, for example:

"While the foregoing disclosure has primarily focused on example therapeutic applications using two-photon excitation of agents with ultrashort pulsed NIR light produced by mode-locked titanium:sapphire lasers, *the present invention is not limited to such excitation nor to such narrowly defined optical sources*. In fact, aspects of the present invention are applicable when optical excitation is effected using linear or other non-linear methods. For example, various other optical sources are applicable, alone or in combination, such as *continuous wave and pulsed* lamps, diode light sources, semiconductor lasers; other types of gas, dye, and solid-state continuous, pulsed, or mode-locked lasers, including: argon ion lasers; krypton ion lasers; helium-neon lasers; helium-cadmium lasers; ruby lasers; Nd:YAG, Nd:YLF, Nd:YAP, Nd:YVO4, Nd:Glass, and Nd:CrGsGG lasers; Cr:LiSF lasers; Er:YAG lasers; F-center lasers; Ho:YAG and Ho:YLF lasers; copper vapor lasers; nitrogen lasers; optical parametric oscillators, amplifiers and generators; regeneratively amplified lasers; chirped-pulse amplified lasers; and sunlight." (p. 22, line 16 - p. 23, line 4)

Accordingly, this passage clearly illustrates that the treatment methods of the present invention include a broad range of sources capable of producing light with temporal properties ranging from continuous wave to ultrashort pulsed. The embodiment of amended Claim 55 is directed to a method for treatment involving continuous or quasi-continuous treatment with light, and in particular to use of those devices which one skilled in the art would understand to be capable of producing light

having a duration of at least 10 microseconds, such as light emitting diodes and diode lasers, ion lasers, continuous and pulsed lamps. Moreover, since such light is applied, for example, by use of optomechanical scanning means, the time over which such light is applied to a particular volume of tissue may also be related to the properties of such scanning means. Details of a preferred embodiment for this scanning means are provided at a number of locations in the specification, such as the following passage:

> "By scanning the location of the focus of the beam 86 throughout the volume of the tumor 88, complete photoactivation of the melanin, melanin precursors, or other endogenous pigments into a phototoxic product throughout the tumor 88 can be effected. This scanning action can be produced by changing the position of the focus 86 relative to the tumor 88, or by moving the tumor 88 relative to a stationary focus 86 location....
>
> "This scanning can be done, for example, by positioning a focus of a beam of light over a range of positions so that a focal plane of the light beam occurs at a site located between a surface of the tissue and a point substantially beyond the tissue surface.... This scanning can further include varying, while the beam of light is extant, the radial position of the focal plane within the tissue, thereby to photoactivate the endogenous pigment at a multiplicity of positions between the tissue surface and a position located substantially beyond the tissue surface." (p. 19, lines 6-21)

Similar description is provided at p. 25, lines 14-15. Since optomechanical scanners typically have maximum resonant frequencies on the order of 10 kHz, one skilled in the art would understand that the resultant application of light would have a duration of at least 10 microseconds (i.e., 1/10,000 Hz). This would be the case whether the light source was continuous wave or mode-locked (i.e., ultrashort pulsed in a quasi-continuous pulse train). Hence, one skilled in the art would understand from the description in the specification that a continuous wave laser source or certain types of pulsed laser sources can be used in the method of the present invention, that for the embodiment

using these types of laser sources, light is applied to the volume of tissue containing the endogenous pigment continuously for a duration of at least 10 microseconds.

Accordingly, for at least the above-stated reasons, it is respectfully submitted that the amendments to independent Claim 55 are supported by the application as filed.

Applicants will now address each of the Examiner's remaining rejections and comments in the order in which they appear in the Office Action.

Claim Rejections – 35 USC §103

Rection over Latina in view of Mourou

In the Office Action, the Examiner rejects Claims 55-69 and 72-74 under 35 U.S.C. §103(a) as being unpatentable over Latina (USP 5,549,596) in view of Mourou et al. (USP 5,656,186). This rejection is respectfully traversed.

In particular, Latina and Mourou (individually or even if properly combined) fail to disclose or suggest the invention of amended independent Claim 55 of the present application. For example, Latina does not disclose or suggest the method of Claim 55 of treatment of tissue using light having an application duration of at least 10 microseconds (μs). Instead, Latina clearly teaches away from such method, as exemplified by the following passage from the reference:

> "*Pulse durations of between about 1 nsec and about 2 μsec may be utilized.* The desired pulse duration is related to the type and size of pigment particle within the target cells to be damaged. Since the thermal relaxation of a particle is related to the particle size of the pigment material, smaller intracellular particles require a shorter pulse duration to ensure confinement of energy to the target cells. *Excessive pulse duration, such as more than five μsec or continuous waves, may cause nonselective killing of both pigmented and nonpigmented cells, as well as disruption of*

> *collagenous structures*; this occurs as the longer laser exposure durations allow heat diffusion and resultant disruption of surrounding nontarget tissues. In contrast, prior art techniques employing ablation of tissue by coagulation utilize distinctly longer radiation durations." (col. 4, lines 5-19, emphasis added)

This passage clearly shows that Latina teaches away from use of illumination having a duration of at least 10 μs (which are purported in the reference to be undesirable and resulting in non-selective killing of cells and damage to non-targeted tissue). These teachings are further reinforced by the experimental data reported by Latina:

> "Using mixed melanized and non-melanized TM cell cultures, selectivity for killing only melanized TM cells was determined at various pulse durations and pulse energies. *Selective killing of pigmented TM cells could not be achieved with pulse durations of 8 μsec or greater.*" (col. 10, lines 32-36, emphasis added)

Thus, Latina reaches the conclusion that the subject matter of USP '596 is not compatible with illumination having a duration of 8 μs or greater as it fails to achieve the desired selective killing of pigmented cells at such duration, and instead, the reference teaches that such a duration kills non-selected and non-pigmented cells.

In contrast, Applicants have successfully tested the present invention with light sources ranging from ultrashort pulsed to continuous wave, and the teachings contained in the specification of the present application are not limited to the range limitations recited in Latina (i.e., use of pulsed illumination of a duration less than 5-8 μs). For example, Applicants have shown that application of light to small volumes of pigmented tissue (i.e., melanoma tumors) for 50 microseconds (i.e., dwell time of 50 μs per point of illumination) leads to selective destruction of such pigmented tissue, with no adverse effect in surrounding normal tissue treated in the same manner with the same light.[2]

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[2] See third and fourth paragraphs, Materials and Methods section of Dees et al., "Treatment Of Murine Cutaneous Melanoma With Near Infrared Light", Photochem. Photobiol.

This light was applied in the form of either a quasi-continuous train of 200 fs mode-locked pulses or a continuous illumination for the entire 50 μs dwell time. Both forms of illumination comprise continuous illumination for at least 10 μs, as recited in amended independent Claim 55 of the present application. The data shown in Table 1 of this reference illustrates that the results were equivalent for both illumination conditions. Such results are in stark contrast to those reported by Latina, which predicts that non-specific tissue damage will occur for light application having a duration of greater than 8 μs, and serves to highlight the unique capabilities of the method of independent Claim 55 over that which is disclosed in Latina.

Since amended independent Claim 55 is directed to an embodiment having a pulse duration outside the range limitations of Latina, Latina, whether alone or in combination with another reference (including Mourou), cannot render obvious the method of independent Claim 55.

Likewise, the teachings of Mourou concern the use of extremely short pulse laser illumination (i.e., less than 1 ps, as noted by the Examiner on p. 4 of the Office Action). Since such excitation is far removed temporally from that claimed in Claim 55, Mourou, whether alone or in combination with another reference (including Latina), cannot render obvious the invention of Claim 55.

Therefore, since both Latina and Mourou describe methods and underlying processes[3] that are fundamentally different than that of independent Claim 55, Latina in view of Mourou cannot render obvious the method of Claim 55 of the present application. Accordingly, this independent

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75(3), (2002) p. 296-301. A copy of this document is being submitted herewith in the enclosed IDS.

[3] The salient differences between the processes underlying the present application and those of Latina and Mourou were described in detail in Applicants' Amendment B.

claim and those claims dependent thereon are patentable over the cited references, and it is respectfully requested that this rejection be withdrawn.

Claim Rejections – 35 USC §103 (Aprile Carpenter in view of Mourou)

In the Office Action, the Examiner rejects Claims 55 and 71 under 35 U.S.C. §103(a) as being unpatentable over Aprile Carpenter (EP 0 649 667 A2) in view of Mourou. This rejection also is respectfully traversed.

More specifically, neither Aprile Carpenter nor Mourou, either individually or combined, disclose or suggest the method of independent Claim 55 of the present application. Further, the combination of these references is improper.

For example, Claim 55 is directed to a method for treatment of tissue containing an endogenous pigment while Aprile Carpenter requires an intravenous injection of a chromophore carrying compound (see e.g. [0027], [0069]-[0072] in reference which shows that the method in the reference only works with the addition of this chromophore which is not an endogenous pigment).[4]

Additionally, Claim 55 recites that the light is produced by a single light source. In contrast, Aprile Carpenter requires a complicated multi-source apparatus (i.e. multiple fiberoptic guided beams). For example, the reference states that:

> "[0056] *The central feature, without which the proper delivery of Enhanced Hyperthermia would not be possible*, and, at the same time one of several technological innovations in the LAILT System, *is the presence of multiple fiberoptic*

[4]The Examiner contends that in "Example 1", Aprile Carpenter discloses tests on a tattoo dye. Applicant notes that this example only appears in European Patent Application EP 0 649 667 A2. In the resulting patent, EP 0 649 667 B1 (a copy attached in enclosed IDS), "Example 1" is no longer included, and there is no mention of the method of the reference being used on a tattoo.

> *guided beams of nearly identical power, originating from distinct individually driven laser energy sources*, which ensure uniform distribution of power within the illuminated region." (emphasis added)

and that this characteristic is "vital" ([0057]). In fact, the reference actually teaches away from a single source of light as stated in the following passage:

> "[0058] Systems equipped with multiple fiberoptic lines, utilizing the electromagnetic energy *originating from one single powerful laser source, cannot allow* for proper control of the output power." (emphasis added)

Further, independent Claim 55 requires scanning with a beam of light. In contrast, Aprile Carpenter does not disclose or suggest scanning with a beam of light. Rather, the reference discloses continuous illumination (see e.g. [0070] illumination for 90 seconds, which one skilled in the art would understand not to be scanning and to be significantly longer than that of the claimed invention). The Examiner admits that the reference does not disclose scanning and cites Mourou for allegedly showing this feature and concludes that it would have been obvious to combine the method of Mourou with Aprile Carpenter to better localize laser induced breakdown.

Applicants respectfully submit that one skilled in the art would not combine the teachings of these two references. For example:

Aprile Carpenter requires using multiple sources of light and teaches away from use of a single light source. Mourou discloses use of a single light source.

Aprile Carpenter has a continuous source of light while Mourou uses a pulsed source of light.

Aprile Carpenter requires additional chromophore and Mourou does not.

Aprile Carpenter has a thermal mechanism and Mourou does not.

In fact, Aprile Carpenter and Mourou teach in opposite directions on each of these key facets, leading to remarkably different methods having very different properties and uses. Mourou teaches

the use of a single focused beam of ultrashort pulses to ablate any kind of material without the need for addition of a chromphore, wherein such method avoids thermal effects. In contrast, April Carpenter teaches use of a multiple source, continuous illumination that requires addition of a chromophore and is based on thermal effects. Combination of these teachings is contradictory and illogical. There is no suggestion or motivation to combine such contrary teachings, and one skilled in the art simply would not do it. Accordingly, the combination of these references is improper.

In addition, the shortcomings of Mourou relative to the presently claimed invention have been described *supra*. Hence, Mourou, whether alone or in combination with another reference (including Aprile Carpenter), cannot render obvious the invention of amended Claim 55.

Therefore, for at least the above-stated reasons, the combination of these references is improper, and even if combined, fail to disclose or suggest the claimed invention. Hence, the claims are patentable over the cited references, and it is respectfully requested that this rejection be withdrawn.

Information Disclosure Statement

Applicants submitted an Information Disclosure Statement (IDS) on March 10, 2005 and are submitting an IDS herewith. It is respectfully requested that these IDSs be entered and considered prior to the issuance of a further action in this application.

Conclusion

For at least the above-stated reasons, it is respectfully submitted that the claims of the present application are in an allowable form and are patentable over the cited references. Accordingly, it is requested that the application now be allowed.

If any fee should be due for this Amendment, please charge our deposit account 50/1039.

Favorable reconsideration is earnestly solicited.

Respectfully submitted,

Date: April 11, 2005

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